

# Clinical Features of Patients with Stage IIIB and IV Bronchioloalveolar Carcinoma of the Lung

Oscar S. Breathnach, M.B.<sup>1</sup>

Naoko Ishibe, Sc.D.<sup>2</sup>

John Williams, M.D.<sup>3</sup>

R. Ilona Linnoila, M.D.<sup>1</sup>

Neil Caporaso, M.D.<sup>2</sup>

Bruce E. Johnson, M.D.<sup>1</sup>

<sup>1</sup> Medicine Branch, Division of Clinical Science, National Naval Medical Center, Bethesda, Maryland.

<sup>2</sup> Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Naval Medical Center, Bethesda, Maryland.

<sup>3</sup> Department of Pathology, National Naval Medical Center, Bethesda, Maryland.

Presented in part at the 34th annual meeting of the American Society of Clinical Oncology, Los Angeles, California, 1998.

Address for reprints: Bruce E. Johnson, M.D., Director, Lowe Center for Thoracic Oncology, The Dana Farber Cancer Institute, Dana 1234, 44 Binney Street, Boston, MA 02115.

Received December 18, 1998; revision received April 9, 1999; accepted April 9, 1999.

**BACKGROUND.** The incidence of bronchioloalveolar carcinoma of the lung (BAC), a pathologically distinct type of nonsmall cell lung carcinoma (NSCLC), appears to be rising. In this study, the authors compared data on the clinical presentation and clinical courses of patients with Stage IIIB and IV BAC with data on other types of NSCLC.

**METHODS.** The authors collected clinical, radiographic, and pathology information about 28 patients with Stage IIIB and IV BAC and 124 patients with other histologic types of NSCLC.

**RESULTS.** Twelve of 28 BAC patients (43%) were women, compared with 40 of 124 control patients (32%). Nine (32%) of the patients with BAC had never smoked cigarettes, versus 20 controls (16%) ( $P = 0.02$ ). Eighteen patients (64%) with BAC had bilateral multilobar or multicentric pulmonary involvement, compared with 13 controls (15%) ( $P < 0.001$ ). Patients with advanced stage (IIIB and IV) BAC had a median survival of 15 months from the time of diagnosis; for patients with other types of Stage IIIB and IV NSCLC, had a median survival of 10 months ( $P = 0.01$ ).

**CONCLUSIONS.** Patients with BAC of the lung have clinical, radiographic, and pathologic characteristics that distinguish them from patients with other types of NSCLC. A greater proportion of women and nonsmokers present with BAC than with other types of NSCLC. Patients with advanced stage BAC are more likely to have bilateral diffuse pulmonary involvement, are less likely to develop brain metastases, and have longer survival than patients with other types of Stage IIIB and IV NSCLC. Further research is warranted to define etiology, molecular abnormalities, and more effective therapeutic interventions. *Cancer* 1999;86:1165-73.

© 1999 American Cancer Society.

**KEYWORDS:** bronchioloalveolar carcinoma, lung carcinoma, carcinoma, nonsmall cell, clinical trials, chemotherapy.

The incidence of bronchioloalveolar carcinoma (BAC) is increasing in frequency and contributes to the higher incidence of adenocarcinoma noted in recent decades.<sup>1-4</sup> The etiology of this increase in the incidence of BAC is undefined. BAC tends to occur more frequently in women and in patients who have never smoked cigarettes.<sup>5,6</sup> Patients with advanced BAC are more likely to have bilateral and multilobar involvement than patients with other types of lung carcinoma.<sup>4</sup>

Reports of patients with resected Stage I lung carcinoma have shown that such patients with BAC live longer than patients with other types of nonsmall cell lung carcinoma (NSCLC).<sup>7,8</sup> However, there is little information about the clinical presentation and course of patients with advanced stage BAC. In view of this, we performed a retrospective review of our consecutive patients with Stage IIIB and IV NSCLC who were treated on therapeutic clinical trials at the Medicine Branch at the National Naval Medical Center. We compared the

clinical presentation and course of our BAC patients with Stage IIIB and IV with those patients with other types of Stage IIIB and IV NSCLC.

## PATIENTS AND METHODS

### Patients

One hundred fifty-two patients with Stage IIIB and IV NSCLC were identified from 4 consecutive therapeutic clinical trials performed at the Medicine Branch of the National Cancer Institute at the National Naval Medical Center between 1983 and 1998.<sup>9-12</sup> Eligibility criteria for the trials included pathologically confirmed NSCLC with measurable or assessable disease, Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ , and no serious concurrent medical or psychiatric problems. Patients with brain metastases were included provided that these metastases had been treated with surgery and/or radiation therapy and that the patient had made a satisfactory, stable recovery.

### Methods

Medical records were retrieved, and information on patient age, gender, performance status, smoking history, symptoms and signs at presentation, radiographic appearances, metastatic sites, stage, therapeutic intervention, initial sites of progressive disease, and survival from the time of diagnosis and from the first day of systemic treatment was abstracted. Radiologic evaluations at the time of initial diagnosis (chest X-ray and computed tomography [CT] of the chest) were collected on the BAC patients and reviewed, because reports may not have described adequately the pattern of disease in these patients. Staging included CT of the chest, with the liver and adrenal glands included in all patients. Bone scans and CT of the brain were performed if there were symptoms, signs, or laboratory abnormalities to suggest the presence of metastatic disease. Patients were assigned a stage based on these investigations.<sup>13</sup> Smokers were defined as those who were actively smoking, exsmokers if they had been off cigarettes for 6 months or more, and nonsmokers if they had no prior history of cigarette smoking.<sup>14</sup>

### Pathology Review

The histology and cytology slides were retrieved and reviewed by two pulmonary pathologists (J.W. and R.I.L.). A consensus was required before classifying the pathology specimens according to their respective histologic type. All cases had been prospectively reviewed to establish the pathologic diagnoses at the time of entry onto the respective treatment protocols.<sup>9-12</sup> The

histologic and cytologic criteria for the diagnosis of BAC have been published previously.<sup>15-21</sup>

The histologic criteria included a peripheral tumor manifesting the growth of well-differentiated cuboidal or columnar tumor cells along intact alveolar walls and no evidence of a primary adenocarcinoma at some extrapulmonary site.<sup>15-19</sup> The cytologic criteria for a diagnosis of BAC included prominence of monolayered tumor sheets, fine chromatin pattern, abundant cytoplasm showing uniformity, a high nuclear-cytoplasmic ratio, and mild cellular pleomorphism.<sup>16,20,21</sup> Nuclear folds are a common finding, and cells nearly always lack cilia.<sup>16</sup> The patients with other types of NSCLC were classified according to the major histologic groups: adenocarcinoma ( $n = 89$ ), large cell carcinoma ( $n = 15$ ), squamous cell carcinoma ( $n = 10$ ), poorly differentiated carcinoma ( $n = 6$ ), carcinoid tumor ( $n = 1$ ), and NSCLC-not otherwise specified ( $n = 3$ ).<sup>17</sup>

### Radiologic Evaluation

The chest radiographs and CT of the chest at presentation were reviewed. The pulmonary findings were classified into 3 groups: solitary pulmonary nodule/mass, consolidation, or diffuse.<sup>22-27</sup> Table 2 outlines the characteristics of the three presentations in both patients with BAC and those with other forms of NSCLC. Patients with solitary pulmonary nodules or focal consolidation included in the analysis had evidence of extrathoracic metastases. Diffuse pulmonary involvement was characterized further as unilateral or bilateral and according to the number of lobes involved. Multicentric involvement is the presence of numerous nodules, with or without consolidation, within the same lobe; whereas multilobar is the presence of multiple nodules, with or without consolidation, within more than one lobe.

### Statistical Methods

The chi-square test was used to assess the univariate association of categorical patient characteristics by case status. Similarly, the Student *t*-test was used to evaluate the association for continuous variables. Two separate comparisons were made: 1) patients with BAC versus those with all other types of NSCLC and 2) BAC patients versus those with adenocarcinoma. All of the *P* values listed were two sided, and significance was assessed at an  $\alpha$  level of 0.05.

The Wilcoxon test was used to compare Kaplan-Meier survival curves. Survival analysis was performed in relation to two time points for each patient, respectively, to contrast survival during these specific intervals. These time-frames spanned from 1) the date of diagnosis and 2) the date of first (systemic) treatment

**TABLE 1**  
**Patient Characteristics**

Characteristic	BAC		NSCLC controls		P value
	No.	%	No.	%	
Patients	28	100	124	100	—
Age (yrs)					
Median	60.5	—	56	—	—
Range	29–80	—	24–79	—	—
Gender					
Male	16	57	84	68	0.3
Female	12	43	40	32	—
Performance status					
0	4	14	10	8	—
1	22	79	98	79	0.48
2	2	7	16	13	—
Smoking history					
Nonsmoker	9	32	20	16	—
Former smoker	10	36	33	27	0.02
Active smoker	8	29	70	56	—
Unspecified	1	4	1	1	—
Histology					
Adenocarcinoma	—	—	89	72	—
Large cell	—	—	15	12	—
Squamous cell	—	—	10	8	—
Poorly differentiated	—	—	6	5	—
Carcinoid	—	—	1	1	—
NSCLC, NOS	—	—	3	2	—
Stage:					
IIIB	4	14	39	31	—
T4	4	—	19	—	—
N3	0	—	20	—	—
IV	21	75	81	65	0.04
Relapsed	3	11	4	3	—

BAC: bronchioloalveolar cell carcinoma; NSCLC: nonsmall cell lung carcinoma; NOS: not otherwise specified.

until either the date of death or the last contact (if alive), up to 24 months after the initiation of therapy. Deaths due to causes other than lung carcinoma ( $n = 8$ ) were treated as censored observations at the time of death.

## RESULTS

### Patient Characteristics

Patient characteristics are listed in Table 1. The 28 patients with advanced BAC had a median age, proportion of females, and good performance status similar to those in patients with other types of NSCLC. The smoking history and stage of disease were different between patients with BAC and patients with other types of lung carcinoma. Nine of the 28 BAC patients (32%) were nonsmokers, compared with only 20 control patients (16%) ( $P = 0.02$ ). The median pack year of cigarette consumption within the BAC smokers (including current and former smokers) was 35, com-

pared with 40 in the NSCLC control group ( $P = 0.048$ ). Four of the 28 patients with BAC (14%) had Stage IIIB disease, compared with 39 patients (31%) with other types of NSCLC ( $P = 0.04$ ). Two of these 4 patients with BAC had pleural effusions (T4 lesion), whereas the other 2 had satellite lesions within the ipsilateral primary-tumor lobe of the lung (T4 lesion). None of the patients with BAC had N3 involvement. The greater frequency of patients with Stage IV BAC reflects the more common disease pattern of bilateral disease at presentation.

### Pathology Review

All patients had their pathologic diagnosis established on their histology and/or cytology specimens at the National Naval Medical Center prior to the initial enrollment onto their therapeutic protocols.<sup>9–12</sup> Pathologic material from all but 2 patients with BAC was available for rereview, which consisted of 27 histologic samples and 2 cytologic samples. The 2 patients who were diagnosed by cytologic examination according to published criteria were included in the study.<sup>16,20,21</sup>

One of the patients who originally was diagnosed with BAC was reclassified with papillary adenocarcinoma and was assigned to the control group, leaving a total of 28 patients with a diagnosis of BAC. The pathology slides and blocks were not retrievable for 2 patients with previously confirmed BAC; they are included in the group of patients with BAC.

The pathology specimens from 91 of the 124 patients with NSCLC other than BAC were retrieved for review. The diagnoses of NSCLC in these patients had all been confirmed previously by pulmonary pathologists in the department in which the current pathology review was performed.<sup>9–12</sup> The patients whose pathology specimens could not be retrieved maintained their initial diagnosis; therefore, they are included with the control patients in this analysis. There were no reassignments of patients from the control group to the bronchioloalveolar cohort. The majority of patients assigned to the control group had a pathologic diagnosis of adenocarcinoma ( $n = 89$ ; 72%). Because no adjustments were necessary within the 91 of 124 pathology slides from control patients, and because all of the slides had been reviewed previously at our center by our pathologists, we believed that it would be appropriate to include all 124 patients within the control group.<sup>9–12</sup>

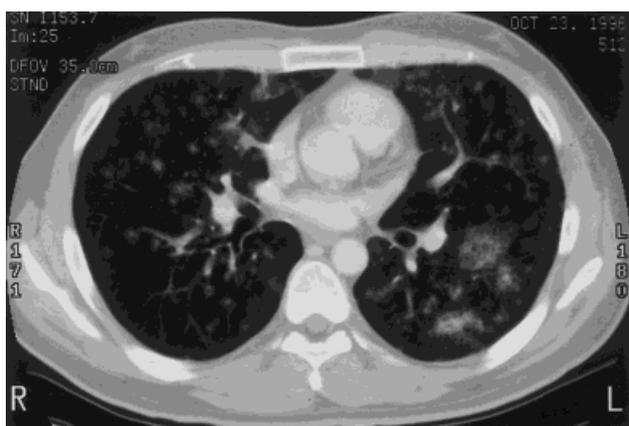
### Symptom Characteristics

Most symptoms of patients presenting with BAC were similar to those seen in patients with other types of NSCLC. However, cough was more common in patients with BAC than in patients with other types of

**TABLE 2**  
Chest Radiographic Characteristics

Characteristic	BAC (n = 28)		NSCLC controls (n = 123)		P value
	No.	%	No.	%	
Solitary lesion <sup>a</sup>	4	14	76	62	<0.001
Consolidation	4	14	2	2	<0.001
Diffuse					
Bilateral multilobar	14	50	11	9	<0.001
Bilateral multicentric	4	14	2	2	<0.001
Unilateral multicentric	0	0	7	6	<0.001
Unilateral multilobar	0	0	4	3	<0.001
Effusion in absence of a lung parenchymal mass	2	7	11	9	0.99
Regional lymph node masses alone	0	0	10	9	0.99

<sup>a</sup> Patients with solitary pulmonary lesion with documented extrathoracic metastatic involvement (Fisher exact test).



**FIGURE 1.** A computerized tomograph of the chest from a male patient age 34 years shows bilateral, multilobar involvement with bronchioloalveolar cell carcinoma.

lung carcinoma (71% vs. 50%;  $P = 0.04$ ). The classic symptom of bronchorrhea was not encountered in our patients with BAC.

### Radiologic Appearances

Three patterns of disease were noted on chest CT scans of patients with BAC: solitary nodule/mass, consolidation, and diffuse pulmonary lesions (Table 2). Patients with solitary pulmonary nodular masses included in this study had documented evidence of extrathoracic metastases.

Patients with BAC had bilateral disease 64% of the time, compared with 11% of control patients ( $P < 0.001$ ). The classic bilateral multilobar presentation was seen in 50% of patients ( $n = 14$ ) with BAC and in 9% of control patients ( $n = 11$ ) (Figs. 1–3). Seventy-six control patients (62%) had solitary pulmonary lesions, compared with 4 patients (14%) with BAC ( $P < 0.001$ ).

### Sites of Metastatic Disease at Initial Presentation

The different patterns in sites of disease between patients presenting with Stage IV BAC and those presenting with other types of NSCLC are reflected by the extent of pulmonary involvement and metastatic disease to the brain or liver. Bilateral pulmonary involvement was present in 16 of 21 patients (76%) with Stage IV BAC and in 11 of 81 control patients (14%) with Stage IV NSCLC. Brain metastases were identified in 1 of 21 patients (5%) with Stage IV BAC, compared with 19 of 81 control patients (24%) with Stage IV NSCLC ( $P = 0.02$ ). Liver metastases were present at diagnosis in 16 of 81 control patients (20%) with Stage IV NSCLC but were not observed in patients with BAC ( $P = 0.04$ ). Adrenal and bone metastases were present in similar proportions in both groups.

### Treatment Profiles

Three patients with BAC were treated with radiation therapy to the brain ( $n = 1$  patient), bone ( $n = 1$  patient), and chest ( $n = 1$  patient) before they started chemotherapy. Forty-three patients with other types of NSCLC were treated with radiotherapy to the brain ( $n = 18$  patients), bone ( $n = 14$  patients), or chest ( $n = 14$  patients). All of the patients with BAC and 117 of the 124 patients with other types of NSCLC (94%) were treated with systemic chemotherapy (see Table 4). Eighty-five percent ( $n = 24$ ) of our patients with BAC received cisplatin-based therapy, compared with 88% ( $n = 103$ ) of patients with NSCLC ( $P = 0.001$ ). More than half of these patients (81 of 127) were treated with continuous 96-hour infusional paclitaxel and bolus cisplatin on either our previously reported Phase I or subsequent Phase II clinical trial.<sup>10,12</sup>

The remaining patients were treated with either an "in-vitro best regimen" using cell lines derived

from the patients (BAC:  $n = 1$  patient; controls:  $n = 14$  patients), etoposide/cisplatin (BAC:  $n = 4$  patients; controls:  $n = 42$  patients), or a Phase I agent (ipomeanol) (BAC:  $n = 3$  patients; controls:  $n = 0$  patients).<sup>9,11</sup> Seven patients in the control group were not treated with any systemic therapy. Six of these 7 patients with NSCLC were treated with local palliative radiation therapy, 4 of whom were treated with thoracic irradiation. The other 2 patients received irradiation to vertebral metastases.

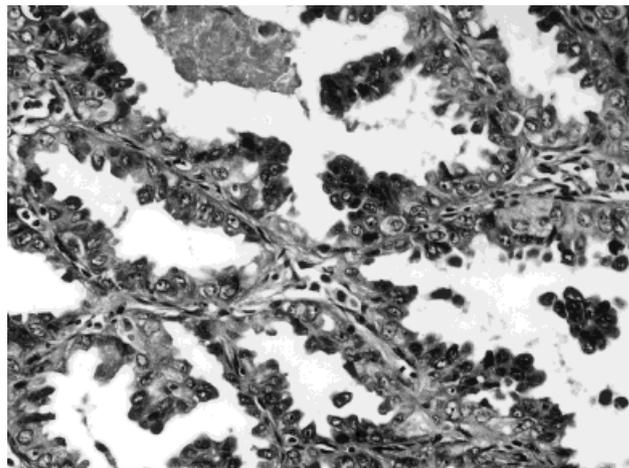
### Disease Progression

The first sites of disease progression were different in patients with BAC than in patients with other types of NSCLC (Table 3). The pulmonary parenchyma was the first site of progression in 14 of 25 patients with BAC (56%), compared with 43 of 116 patients with other types of lung carcinoma (37%) ( $P = 0.06$ ). Fourteen of 116 patients with NSCLC other than BAC (12%) initially progressed in the liver, and 32 of 116 (28%) developed progressive pleural effusions. None of the patients with BAC initially progressed in the liver or pleura. The brain was the first site of progression in 23 of 116 patients with NSCLC (20%), compared with 2 of 25 patients with BAC (8%). At the time of analysis, 2 of the BAC patients and 5 of the patient controls had unspecified sites of progressive disease. Another 3 patients with NSCLC and 1 patient with BAC had no evidence of progressive disease.

### Survival

Patients with BAC lived longer than the patients with adenocarcinoma and other types of NSCLC for both Stage IV (see Table 5) and Stages IIIB and IV combined. Statistically significant differences in survival comparing Stage IV BAC with patients with Stage IV adenocarcinoma (see Table 5) were noted in relation to survival from time of diagnosis (15.2 months vs. 10.4 months;  $P = 0.027$ ) and survival from the time of first therapy (11.6 months vs. 7.7 months;  $P = 0.04$ ). The median and 1-year survival rates for patients with Stage IV BAC compared with patients with Stage IV NSCLC demonstrate a statistically significant survival advantage for patients with BAC in terms of survival from the time of initial diagnosis (15.2 months vs. 9.7 months;  $P = 0.007$ ), the time from first therapy (11.6 months vs. 6.8 months;  $P = 0.008$ ), and the time from first systemic therapy (11.7 months vs. 7.5 months;  $P = 0.011$ ).

Patients with BAC, Stages IIIB and IV combined, had a longer median survival from the time of diagnosis to death at 15.2 months (95% confidence interval [CI], 12.4–18.2) compared with 9.9 months (95% CI, 8.4–11.2) in similar stage NSCLC control patients ( $P =$



**FIGURE 2.** A photomicrograph of a histologic section from a peripheral lung biopsy demonstrates bronchioloalveolar cell carcinoma of the lung from the patient shown in Figure 1 (H & E, original magnification,  $\times 250$ ).

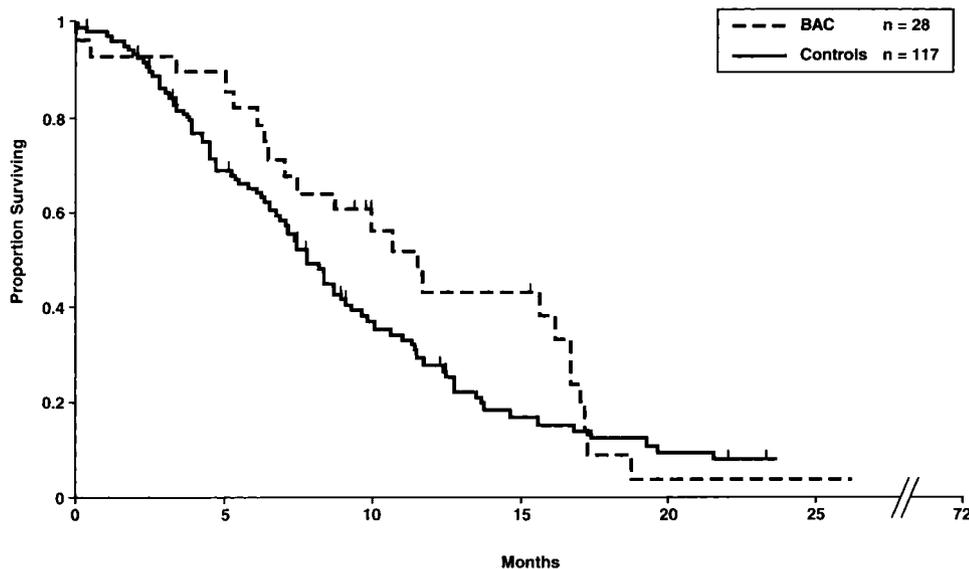
0.01). The median survival duration from first systemic chemotherapy was longer for patients with Stage IIIB and IV BAC (11.7 months; 95% CI, 8.7–16.7) compared with patients of similar stage with other types of NSCLC (8.3 months; 95% CI, 6.8–9.7;  $P = 0.04$ ). The median survival for patients with Stage IIIB and IV adenocarcinoma from the initiation of first systemic therapy was 9.7 months (95% CI, 7.7–11.7;  $P = 0.25$ ). The 1-year survival rates for BAC and controls from the time of first systemic therapy were 47.7% and 29%, respectively ( $P = 0.15$ ).

The median survival times from the start of initial therapy (either radiation or chemotherapy) were 11.7 months (95% CI, 8.7–16.7) and 7.8 months (95% CI, 6.7–9.2) in the patients with Stage IIIB and IV BAC and the NSCLC control group, respectively ( $P = 0.03$ ). The 1-year actuarial survival rates were 47% and 28% for the BAC and NSCLC control patients, respectively ( $P = 0.1$ ).

The survival rates for the 81 patients treated with 4-day infusion of paclitaxel plus cisplatin also were analyzed. The median survival times from the initial therapy for the 20 patients with Stage IIIB and IV BAC were modestly longer (16.1 months; 95% CI, 8.9–17) than for the 61 patients with NSCLC other than BAC (9.2 months; 95% CI, 7.5–12.8;  $P = 0.18$ ). The 1-year survival rates from first therapy for BAC and control patients were 57% and 37%, respectively ( $P = 0.16$ ).

### DISCUSSION

The incidence of BAC is increasing and is believed to contribute to the dramatic rise in incidence that now makes adenocarcinoma the most common form of NSCLC.<sup>1–4</sup> The original descriptions of BAC report



**FIGURE 3.** Actuarial survival from the time of first systemic therapy is shown for patients with advanced bronchioloalveolar cell carcinoma (BAC) and other types of nonsmall cell lung carcinoma.

**TABLE 3**  
Sites of First Progressive Disease

Characteristic	BAC (n = 25) <sup>a</sup>		NSCLC controls (n = 116) <sup>a</sup>		P value
	No.	%	No.	%	
Lung parenchyma	14	56	43	37	0.06
Bone	4	16	23	20	0.79
Thoracic lymph nodes	3	12	31	27	0.13
Brain	2	8	23	20	0.17
Adrenals	1	4	2	2	0.46
Skin	1	4	3	3	0.46
Breast	1	4	0	0	0.19
Pleural effusions	0	0	32	28	0.001
Liver	0	0	14	12	0.07
Retroperitoneal lymph nodes	0	0	1	1	0.99
Falling PS	2	8	7	6	0.67

PS: performance status.

<sup>a</sup> Two of the patients with bronchioloalveolar cell carcinoma (BAC) had unspecified sites of progression, and a third patient had not yet progressed. In comparison, 3 of the nonsmall cell lung carcinoma (NSCLC) control patients had not yet progressed, and 5 others had unspecified sites of progressive disease.

patients with advanced bilateral pulmonary tumors.<sup>15,28</sup> More recent studies on BAC focus on patients with early stage disease. This study adds information about symptoms, sites of disease at presentation and at initial progression, and survival of patients with Stage IIIB and IV BAC. We compared these patients with patients who had similar stage NSCLC and those with adenocarcinoma.

The disease free survival and overall survival rates for patients with both early (Stages I-IIIa) and advanced (Stages IIIB and IV) BAC appear to be longer

**TABLE 4**  
Chemotherapy Regimens Received by Patients with Stage IIIB/IV Bronchioloalveolar Cell Carcinoma and Other Forms of Nonsmall Cell Lung Carcinoma

Chemotherapy regimen	No. of patients with BAC (%)	No. of patients with NSCLC (%)
Paclitaxel/cisplatin	20 (71)	61 (52)
Etoposide/cisplatin	4 (14)	42 (36)
"Best in vitro" agents <sup>a</sup>	1 (4)	14 (12)
Ipomeanol	3 (11)	0 (0)

BAC: bronchioloalveolar cell carcinoma; NSCLC: nonsmall cell lung carcinoma.

<sup>a</sup> Shaw et al., 1993.<sup>9</sup>

than for patients with other types of NSCLC. These were evaluated according to median survival; 1-, 2-, and 5-year survival plus relative relapse; and mortality rates.<sup>7,8,19,29-37</sup> Retrospective confirmation of the pathologic diagnoses of the tumors from these patients was performed in only a minority of these prior studies.<sup>10,33,37-39</sup> All but 2 of our patients with BAC and 91 of the 124 patient controls had their tissue samples reviewed at the time of preparation of this article.

Our 28 patients with Stage IIIB and IV BAC lived 3-5 months longer (an increase of ≈50%) than the patients with other types of NSCLC from the time of diagnosis, the time of initial therapy, or the time from initiation of chemotherapy. Patients with Stage IV BAC also lived 3-5 months longer than patients with other types of NSCLC at a similar stage.

One other study compared the survival of patients with advanced BAC patients with those with other types of NSCLC. In contrast to our findings, those authors reported that 223 patients with metastatic

**TABLE 5**  
Survival Data for Stage IV Patients: Median Survival and 1-Year Survival Rates

	Median survival			1-year survival	
	Months	95% C.I.	P value	%	P value
From time of diagnosis <sup>a</sup>					
BAC (n = 21)	15.2	10.4–18.2		66.7	—
Controls (n = 81)	9.7	7.0–10.8	(0.007)	32.9	0.005
Adenocarcinoma (n = 52)	10.4	7.1–12.4	(0.027)	38.0	0.027
From first systemic therapy <sup>b</sup>					
BAC (n = 21)	11.7	8.7–17.0		47.6	—
Controls (n = 76)	7.5	5.4–9.1	(0.011)	22.4	0.025
Adenocarcinoma (n = 47)	8.8	6.8–11.3	(0.067)	28.3	0.122
From paclitaxel/cisplatin <sup>c</sup>					
BAC (n = 17)	12.2	8.9–17.0		56.3	—
Controls (n = 42)	8.9	7.5–11.6	(0.084)	30.6	0.079
Adenocarcinoma (n = 28)	11.3	7.8–21.5	(0.37)	43.5	0.433

BAC: bronchioloalveolar cell carcinoma; CI: confidence interval.

<sup>a</sup> Survival time from date of diagnosis to time of death.

<sup>b</sup> Survival time from date of first systemic chemotherapy.

<sup>c</sup> Survival time from initiation of 96-hour continuous paclitaxel infusion with bolus cisplatin on Day 5.<sup>10,12</sup>

adenocarcinoma lived longer (6 months) than the 25 patients with metastatic BAC (4 months), although statistical significance was not reached ( $P = 0.64$ ).<sup>29</sup> However, their patients are not directly comparable to the patients reported here, because the majority of their patients with BAC had been treated previously, and one-third of the patients had a poor performance status (2 or 3). Potential explanations for the prolonged survival in our BAC patients compared with prior reports of patients with similar stages of BAC include more selective efficacy of paclitaxel for the treatment of patients with BAC (received by 71% of BAC patients), more asymptomatic patients at initial presentation (14% vs. 4%), more patients with good performance status, and less common prior surgical resection rates (10% vs. 39–44%).<sup>29,40</sup> A longer natural history also may contribute to the prolonged survival observed in these patients with BAC.

Four studies reported 2-year survival rates for advanced BAC patients of 5–8%, which is similar to the 2-year survival rate of 7% observed in our patients with BAC.<sup>19,29,34,36</sup> The other studies of 9–40 patients with advanced BAC reported median survivals of 3–18 months, but their survival information is difficult to interpret, because they did not present survival information about comparable patients with other types of NSCLC.<sup>34,36,39</sup>

The survival of patients with Stage I–III BAC also appears to be longer than for patients with other types of NSCLC. Four studies compared the 5-year survival rates of patients with Stage I BAC<sup>8,33</sup> (n = 33, 67) or Stage I, II, and III BAC<sup>7,32</sup> (n = 235, 33) with that of

patients with similar stages of NSCLC (n = 1618). Patients with Stage I BAC had a 5-year survival rate of 77–85%, compared with 70% for patients with squamous cell carcinoma, 56–66% for patients with large cell carcinoma, and 59–65% for patients with adenocarcinoma.<sup>8,33</sup> The 5-year survival rates for patients with Stage I–III BAC were 55–58%, compared with 18–47% for patients with similar stages of adenocarcinoma.<sup>7,32</sup> The overall mortality rate per year for patients with Stage I–III BAC was 12%, compared with 16% for the patients with adenocarcinoma at a similar stage ( $P < 0.00008$ ).<sup>7</sup> Thus, patients with similar stages of BAC (both early and advanced stage) have a longer survival than patients with other types of NSCLC.

Information documenting differences in patients characteristics, symptoms, disease sites, and response rates to chemotherapy in patients with BAC and those with other types of NSCLC is presented in this article. Our patients with advanced bronchioloalveolar cell carcinoma showed the previously described excess of females and nonsmokers, with a peak incidence within the sixth decade of life.<sup>41</sup> Significant differences in symptoms at presentation between our patients with advanced stage BAC and patients with other forms of NSCLC are less common neurologic symptoms (4% vs. 15%) and more common cough (71% vs. 50%), respectively. Neurologic symptoms also were less common and cough was more common in 25 patients with metastatic BAC compared with 223 patients with metastatic adenocarcinoma reported by Feldman et al.<sup>29</sup>

One previous report in the literature identified

sites of metastatic disease at presentation in patients with advanced BAC.<sup>29</sup> Our data as well as the data in this previous report corroborate the high frequency of diffuse pulmonary involvement (72% and 76%), moderate frequency of skeletal metastases (24% and 28%), and rare brain metastases (4% and 8%) in patients with advanced BAC at initial presentation. Statistically significant differences in the sites of metastatic disease at presentation in patients with BAC, compared with those with other types of NSCLC, were identified at 3 locations: more common bilateral lung involvement, less frequent brain metastases, and less common liver involvement, respectively. Diffuse, bilateral disease was >4-fold more common in the patients with BAC than in patients with other types of NSCLC.

Information about sites of first progression of disease are not provided in prior reports. Progression most often occurs at the site of initial carcinoma involvement, as anticipated. Development or progression of brain metastases ranks as the most dramatic difference between patients with BAC (8%) and patients with other types of NSCLC (20%). Progression also was less common in BAC patients within intrathoracic lymph nodes (12% vs. 27%) and was not seen within the liver. The lungs were identified as the most common site of first progression. These data show the propensity for BAC to spread within the thoracic cavity in contrast to the usual pattern of extrathoracic progression in patients with other types of adenocarcinoma.

Therapeutic modalities for patients with advanced BAC reported in the literature range from attempted surgical resections with or without adjuvant radiation or chemotherapy to chemotherapy alone.<sup>28,29,31,34,37,39,42</sup> Two previous studies have documented the therapeutic efficacy of systemic chemotherapy in patients with advanced BAC and those with other types of NSCLC.<sup>29,37</sup> Patients with both BAC and other types of NSCLC were treated with cisplatin-based regimens in one of the studies. Forty-eight percent of the patients with advanced BAC in the latter study had received no prior therapy. This differs from our patients with advanced BAC, of whom 90% had received no prior systemic therapy.<sup>29</sup>

Response rates of 30–32% have been reported in patients with advanced BAC who were treated with systemic chemotherapy.<sup>29,37</sup> Twenty patients with advanced BAC and 61 patients with advanced NSCLC included in our data were treated with 96-hour infusion paclitaxel and bolus cisplatin chemotherapy. The response rates in these patients with advanced stage BAC and NSCLC were 21% and 47%, respectively ( $P = 0.04$ ). It is difficult to use the standard bidimensional criteria to calculate response rates of measur-

able disease in patients with multifocal BAC, because most patients (78%) have either bilateral diffuse pulmonary involvement (64%) or consolidation (14%). The true proportion of patients with radiographic improvement and clinical benefit may be higher.

Our data confirm advanced BAC as a tumor with a specific tendency for intrapulmonary spread, with limited regional lymph node involvement, and with a reduced tendency for extrathoracic metastases, particularly to the brain and liver. Studies generally show that BAC is moderately sensitive to chemotherapy, with response rates from 20% to 32% and a 1-year survival that is significantly better than that for patients with NSCLC.<sup>29,37,40</sup> These retrospective data suggest that the presentation, response to systemic treatment, and survival differ from those of patients with other types of NSCLC. There is a need for prospective studies to define the clinical presentation and course of patients with BAC. Two current prospective studies evaluate paclitaxel in the setting of advanced BAC: one as a 96-hour continuous infusion (Southwest Oncology Group-9714) and the other as a 3-hour infusion (European Organization for Research and Treatment of Cancer-08956). Further studies will be required and should be integrated with epidemiologic and genetic analyses to fully appreciate and understand the nature of this unique carcinoma.

## REFERENCES

1. Travis WD, Lubin J, Ries L, Devesa S. United States lung carcinoma incidence trends: declining for most histologic types among males, increasing among females. *Cancer* 1996; 77:2464–70.
2. Travis W, Travis L, Devesa S. Lung cancer. *Cancer* 1995;75: 191–202.
3. Auerbach O, Garfinkel L. The changing pattern of lung carcinoma. *Cancer* 1991;68:1973–7.
4. Barsky SH, Cameron R, Osann KE, Tomita D, Holmes EC. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. *Cancer* 1994;73:1163–70.
5. Morabia A, Wynder EL. Relation of bronchioloalveolar carcinoma to tobacco [see comments]. *BMJ* 1992;304:541–3.
6. Barkley JE, Green MR. Bronchioloalveolar carcinoma. *J Clin Oncol* 1996;14:2377–86.
7. Grover FL, Piantadosi S. Recurrence and survival following resection of bronchioloalveolar carcinoma of the lung—the Lung Cancer Study Group experience. *Ann Surg* 1989;209: 779–90.
8. Kwiatkowski D, Harpole D, Godleski J, Herdon JE, Shieh DB, Richards W, et al. Molecular pathologic substaging in 244 Stage I non-small-cell lung cancer patients: clinical implications. *J Clin Oncol* 1998;16:2468–77.
9. Shaw G, Gazdar A, Phelps R, Linnoila RI, Ihde DC, Johnson BE, et al. Individualized chemotherapy for patients with non-small cell lung cancer determined by prospective identification of neuroendocrine markers and in vitro drug sensitivity testing. *Cancer Res* 1993;53:5181–7.

10. Georgiadis M, Schuler B, Brown J, Kieffer LV, Steinberg SM, Wilson WH, et al. Paclitaxel by 96-hour continuous infusion in combination with cisplatin: a Phase I trial in patients with advanced lung cancer. *J Clin Oncol* 1997;15:735-43.
11. Kasturi V, Dearing M, Piscitelli S, Russell EK, Sladek GG, O'Neil K, et al. Phase I study of a five-daily dose schedule of 4-ipomeanol in patients with non-small cell lung cancer. *Clin Cancer Res* 1998;4:2095-102.
12. Georgiadis M, Breathnach O, Schuler B, Kelley MJ, Pizzella P, O'Neil K, et al. Phase II trial of paclitaxel by 96-hour continuous infusion in combination with cisplatin for patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998;17:469a.
13. Mountain CF. Revisions in the international system for staging lung cancer [see comments]. *Chest* 1997;111:1710-7.
14. Tucker M, Murray N, Shaw E, Ettinger DS, Mabry M, Huber MH, et al. Second primary cancers related to smoking and treatment of small cell lung cancer. *J Natl Cancer Inst* 1997;89:1782-8.
15. Liebow A. Bronchiolo-alveolar carcinoma. *Adv Intern Med* 1960;10:329-58.
16. Colby T, Koss M, Travis W. Bronchioloalveolar carcinoma. Atlas of tumor pathology: tumors of the lower respiratory tract, vol. 13. Washington DC: Armed Forces Institute of Pathology, 1995.
17. Organization WH. The World Health Organization histological typing of lung tumors. *Am J Clin Pathol* 1982;77:123-36.
18. Linnoila R, Aisner S. Pathology of lung cancer: an exercise in classification. In: Johnson B, Johnson D, editors. Lung cancer. New York: Wiley-Liss, Inc., 1995;73-95.
19. Clayton F. The spectrum and significance of bronchioloalveolar carcinomas. *Pathol Annu* 1988;23:361-94.
20. Auger M, Katz RL, Johnston DA. Differentiating cytological features of bronchioloalveolar carcinoma from adenocarcinoma of the lung in fine-needle aspirations: a statistical analysis of 27 cases. *Diagn Cytopathol* 1997;16:253-7.
21. Zaman SS, van Hoesen KH, Slott S, Gupta PK. Distinction between bronchioloalveolar carcinoma and hyperplastic pulmonary proliferations: a cytologic and morphometric analysis. *Diagn Cytopathol* 1997;16:396-401.
22. Bonomo L, Storto ML, Ciccosto C, Polverosi R, Merlino B, Bellelli M, et al. Bronchioloalveolar carcinoma of the lung. *Eur Radiol* 1998;8:996-1001.
23. Lee KS, Kim Y, Han J, Ko EJ, Park CK, Primack SL. Bronchioloalveolar carcinoma: clinical, histopathologic, and radiologic findings. *Radiographics* 1997;17:1345-57.
24. Austin JH, Muller NL, Friedman PJ, Hansell DM, Naidich DP, Remy-Jardin M, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. *Radiology* 1996;200:327-31.
25. Webb W, Muller N, Naidich D. Standardized terms for high-resolution computed tomography of the lung: a proposed glossary. *J Thorac Imaging* 1993;8:167-75.
26. Hill CA. Bronchioloalveolar carcinoma: a review. *Radiology* 1984;150:15-20.
27. Akata S, Fukushima A, Kakizaki D, Abe K, Amino S. CT scanning of bronchioloalveolar carcinoma: specific appearances. *Lung Cancer* 1995;12:221-30.
28. Ludington L, Verska J, Howard T, Kypridakis G, Brewer L. Bronchiolar carcinoma (alveolar cell), another great imitator: a review of 41 cases. *Chest* 1972;61:622-8.
29. Feldman ER, Eagan RT, Schaid DJ. Metastatic bronchioloalveolar carcinoma and metastatic adenocarcinoma of the lung: comparison of clinical manifestations, chemotherapeutic responses, and prognosis. *Mayo Clin Proc* 1992;67:27-32.
30. Dumont P, Gasser B, Rouge C, Massard G, Wihlm J. Bronchoalveolar carcinoma: histopathologic study of evolution in a series of 105 surgically treated patients. *Chest* 1998;113:391-5.
31. Greco R, Steiner R, Goldman S, Cotler H, Patchefsky A, Cohn H. Bronchioloalveolar cell carcinoma of the lung. *Ann Thorac Surg* 1986;41:652-6.
32. Heikkila L. Results of surgical treatment in bronchioloalveolar carcinoma. *Ann Chir Gynaecol* 1986;75:183-91.
33. Williams D, Pairolero P, Davis C, Bernatz PE, Payne WS, Taylor WF, et al. Survival of patients surgically treated for Stage I lung cancer. *J Thorac Cardiovasc Surg* 1981;82:70-6.
34. Harpole D, Bigelow C, Glenn Young W Jr., Wolfe W, Sabiston D Jr. Alveolar cell carcinoma of the lung: a retrospective analysis of 205 patients. *Ann Thorac Surg* 1988;46:502-7.
35. Donaldson J, Kaminsky D, Elliott R. Bronchiolar carcinoma: report of 11 cases and review of the literature. *Cancer* 1978;41:250-8.
36. Hsu CP, Chen CY, Hsu NY. Bronchioloalveolar carcinoma. *J Thorac Cardiovasc Surg* 1995;110:374-81.
37. Sorensen JB, Hirsch FR, Olsen J. The prognostic implication of histopathologic subtyping of pulmonary adenocarcinoma according to the classification of the World Health Organization. An analysis of 259 consecutive patients with advanced disease. *Cancer* 1988;62:361-7.
38. Kemeny M, Block L, Braun D, Martini N. Results of surgical treatment of carcinoma of the lung by stage and cell type. *Surg Gynecol Obstet* 1978;147:865-71.
39. Dunn D, Hertel B, Norwood W, Nicoloff DM. Bronchioloalveolar cell carcinoma of the lung: a clinicopathological study. *Ann Thorac Surg* 1978;26:241-9.
40. Marcq M, Galy P. Bronchioloalveolar carcinoma. Clinicopathologic relationships, natural history, and prognosis in 29 cases. *Am Rev Respir Dis* 1973;107:621-9.
41. Falk RT, Pickle LW, Fonham ET, Greenberg SD, Jacobs HL, Correa P, et al. Epidemiology of bronchioloalveolar carcinoma. *Cancer Epidemiol Biomarkers Prev* 1992;1:339-44.
42. James E, Schuchmann G, Hall R, Patterson J, Gillespie J, Gomez A. Preferred surgical treatment for alveolar cell carcinoma. *Ann Thorac Surg* 1976;22:157-62.